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10/579,543	05/15/2006	Per Sonne Holm	BOH06278P00210US	7495

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,543	HOLM, PER SONNE	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *104-117* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *104-117* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/22/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 104-117 are pending and under consideration. The amendment has been entered. Claims 1-103 are canceled.

Claim Objections

Claims 5, 6, 8, 9-24, 27-29, 32, 35-36, 39, 41-42, 44, 46-51, 54 objection to under 37 CFR 1.75(c) as being in improper form because multiple dependent claims cannot depend from any other multiple dependent claim is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 108 and 109 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 108 recite the limitation "YB-1" in the first line. There is insufficient antecedent basis for this limitation in the claim.

Claim 109 recite the limitation "E2 late promoter" in the first line. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5, 24-29, 32, 36, 47-48, 50-54 rejection under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Applicants claim, in claims 1-5, an adenovirus, which can be a naturally occurring adenovirus, wherein the first protein is expressed prior to the second protein is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by
another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-17, 21-27, 29-34, 36-38, 46-54 rejection under 36 U.S.C. 102(b) as being anticipated by Hallenbeck et al (US 5,998,205) is withdrawn in view of the amendment.

Claims 39-40 rejection under 35 U.S.C. 102(a) and (e) as being anticipated by Irving et al (US 20030095989) is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 104-117 are rejected under 35 U.S.C. 103(a) as being unpatentable over by **Steegenga et al,** (Oncogene, 16: 349-357, 1998 (IDS) in view of **Holm et al** (JBC 277(12): 10427-10434, Published, JBC Papers in Press, January 11, 2002 (IDS); **Steenenga et al,** (Molecular and Cellular Biology, 19(5): 3885-3894, 1999).

Steegenga et al, teach a recombinant adenovirus, wherein infection into Hep3B cells with the adenovirus that expresses a first polypeptide comprising E1B and E4orf6 and the second E1A polypeptide (figure 6, page 354). Steegenga teaches apart from the large E1B protein the adenovirus early region encodes the E1A and E4orf6 proteins which have been reported to affect p53 expression as well as its functioning (abstract). After infection with wild-type adenovirus we observed a dramatic decrease in wild-type p53 expression while no down-regulation of p53 could be detected after infection with the E1B virus (abstract). Steegenga et al, teach the different effects of the wild-type adenovirus and E1B adenovirus on p53 expression were not only found in cells expressing wild-type p53 but were also observed when tumor cells expressing highly stabilized mutant p53 were infected with these two viruses (abstract). Infection with different adenovirus mutants indicated the importance of a direct interaction between p53 and the large E1B protein for reduced p53 expression after infection. Moreover, coexpression of the E4orf6 protein was found to be required for this phenomenon, while expression of E1A is dispensable. In addition, Steegenga et al, teach that p53 is actively degraded in wild-type adenovirus-infected cells but not in E1B -infected cells. **Steegenga**

differs from the present invention for not teaching the E4 polypeptide is expressed prior to the E1B polypeptide for inactivation of p53 in combination with a third polypeptide comprising YB-1 polypeptide that is not E1A.

However, at the time of the instant invention **Holm et al** (JBC 277(12): 10427-10434, Published, JBC Papers in Press, January 11, 2002) teaches that YB-1 relocates to the nucleus in adenovirus-infected cells and facilitates viral replication by inducing E2 gene expression through the E2 late promoter (title). Holm teaches that that E1B-55kDa is involved in targeting the transcription factor YB-1 to the nuclei of adenovirus type 5-infected cells where it is associated with viral inclusion bodies believed to be sites of viral transcription and replication (abstract). The YB-1 facilitates E2 gene expression through the E2 late promoter thus controlling E2 gene activity at later stages of infection (abstract). The role of YB-1 for adenovirus replication was demonstrated with an E1-minus adenovirus vector containing an YB-1 transgene. In infected cells, AdYB-1 efficiently replicated and produced infectious progeny particles. Holm et al teach adenovirus E1B-55kDa protein and the host cell factor YB-1 act jointly to facilitate adenovirus replication in the late phase of infection (abstract) as recited in claim 104 of the instant invention. Holm teaches with the transient reporter gene assays (Fig. 6) E1B-55kDa is involved in controlling adenovirus DNA replication at later stages of infection (p 10432, 2nd column, 2nd paragraph). Holm teaches that YB-1 facilitates adenovirus DNA replication by controlling E2 gene transcription via the E2 late promoter. Holm suggests the YB-1 as an E1B-55kDa-dependent cellular factor that controls E2 late promoter activity and in consequence viral DNA replication at later stages of infection (p 10433, 2nd column, last paragraph). Holm suggests these findings are fundamental for adenovirus biology and form a basis for the development of tumor selective adenovirus vectors for cancer gene therapy (p 10433, 2nd column, last paragraph, bridge to p 10444). Steegenga et al, (Molecular and Cellular

Biology, 19(5): 3885-3894, 1999) supplements the teachings to Steegenga et al (1998) by teaching that there is a distinct regulation of p53 and p73 activity by adenovirus E1A, E1B, E4orf6 and E1A12S proteins (p 3886-3892). Steegenga et al suggest in the early phase of Ad infection, when those early proteins are expressed, distinct Ad E proteins are involved in inhibition of the transcription activation by both p53 and p73, although an effect on p73 activity during Ad infection has not been proven directly (p 3893, 2nd column 5th paragraph). Steegenga et al conclude that the E1A proteins including E1A12S seem to have a similar effect on p53 and on p73, but these proteins are differently affected by the large E1B and E4orf6 proteins (p 3894, 1st column). However, the final effect is that both the p53 and the p73 proteins are functionally inactivated as a result of both infection and transformation by Ad (p 3894, 1st column). Apart from the p73 gene, the p53 family contains at least one other member: the KET/p51/p40/p63 protein and it will be interesting to investigate whether the different forms of this p53 homologue can be inactivated by the Ad E proteins as well (p 3894, 1st column). As such Holm/ Steegenga (1999) provide sufficient motivation for one of ordinary skill in the art to apply the first polypeptide comprising E1B and E4orf6 and the second E1A polypeptide adenovirus of Steegenga (1998) to the AdYB-1 construct of Holm/ Steegenga (1999) for study of the function of those genes in the early and late phase of infection.

Accordingly, in view of the teachings of Holm et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the construct of Holm by use of the adenovirus that expresses a first polypeptide comprising E1B and E4orf6 and the second E1A polypeptide in a normal cell with a reasonable expectation of success. One of ordinary of skill in the art would have been motivated to study if both E1B and E4orf6 bound to p53 its conformation is changed in such a way that the protein is sensitized for proteolytic cleavage as taught by Steenenga et al, by using al three polypeptides as in the

claimed invention (p 355, 1st column, last paragraph). One of ordinary of skill in the art would have been particularly motivated for such a modification particularly in view of **Steegenga et al,** (Molecular and Cellular Biology, 19(5): 3885-3894, 1999) that teaches there is a distinct regulation of p53 and p73 activity by adenovirus E1A, E1B, E4orf6 and E1A12S proteins and suggest in the early phase of Ad infection, when those early proteins are expressed, distinct Ad E proteins are involved in inhibition of the transcription activation by both p53 and p73, and that the E1A proteins seem to have a similar effect on p53 and on p73, but these proteins are differently affected by the large E1B and E4orf6 proteins and it will be interesting to investigate whether the different forms of this p53 homologue can be inactivated by the Ad E proteins as well (p 3894, 1st column).

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Claim **115** is rejected under 35 U.S.C. 103(a) as being unpatentable over by Steegenga et al, (Oncogene, 16: 349-357, 1998 (IDS) in view of Holm et al (JBC 277(12): 10427-10434, Published, JBC Papers in Press, January 11, 2002 (IDS); Steenenga et al, (Molecular and Cellular Biology, 19(5): 3885-3894, 1999) and further in view **of Li et al,** (Cancer Research, 61: 6428-6436, 2001).

The teachings of Steegenga (1998)/Holm/Steenenga (1999) are applied here as stated above.

However Steegenga (1998)/Holm/Steenenga (1999) do not teach an IRES sequence, wherein the IRES sequence separates the nucleic acid sequences encoding the first and second polypeptides.

However, at the time of the instant invention **Li et al** teach an AFP-E1AIRES-E1B bicistronic expression cassette fulfilled the necessary requirements and created an AFP-

producing hepatoma-specific adenovirus variant, CV890, for additional clinical development (p 6.428, 2nd column, 2nd paragraph). Li teaches a tumor-specific adenovirus by linking two essential viral genes, *E1A* and *E1B,* with an IRES . Use of an AFP TRE-E1A-IRES-E1B cassette yields a virus of very high specificity for target cells (5,000–100,000:1) with only a single tumor-specific transcriptional regulatory element (TRE) (p 6.428, 2nd column, 2nd paragraph). The TRE-E1A-IRES-E1B bicistronic cassette strategy saves space within the virus genome allowing the reincorporation of the adenovirus E3 region adding much needed antitumor efficacy in vivo and in vitro (p 6.428, 2nd column, 2nd paragraph). As such Li provide sufficient motivation for one of ordinary skill in the art to apply the IRES sequences to the sequences of Steegenga (1998)/Holm/Steenenga (1999) in order to target specific cells in vitro for the studying if there is a distinct regulation of p53 and p73 activity by adenovirus E1A, E1B, E4orf6 and E1A12S proteins in the early phase of Ad infection, when those early proteins are expressed, distinct Ad E proteins are involved in inhibition of the transcription activation by both p53 and p73 as suggested by the teachings of Steegenga (1998)/Holm/Steenenga (1999).

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-54 rejection under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

Statutory Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-3 provisional rejection under 35 U.S.C. 101 as claiming the same invention as that of claims 89-91 of copending Application No. 10/531,366 is withdrawn in view of the amendment.

Claims **104-117** are provisionally rejection under 35 U.S.C. 101 as claiming the same invention as that of claims 179-182, 184-187, 191-196 of copending Application No. 10/531,366

Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985); In re Van Omum, 686 F.2d 937,214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ'644 (CCPA 1969). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321 (d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 39-40 provisional rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 47-48 of copending Application No. 10/451,210 (hereafter the '210 application) is withdrawn in view of the amendment.

Claims 104-117 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 179-196 of copending Application No. 10/451,210 (hereafter the '210 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite an adenovirus comprising a nucleic acid sequence encoding YB-I. The instant claim 104 recites a recombinant adenovirus, wherein upon infection of an eukaryotic cell, the adenovirus expresses a first polypeptide comprising an E1B and E4 polypeptide prior to expressing a second polypeptide comprising an E1A polypeptide, whereby the E4 polypeptide is expressed prior to the E1B polypeptide, while the '210 claims recite recombinant adenovirus, wherein upon infection of an eukaryotic cell, the adenovirus expresses a first polypeptide comprising an E1B polypeptide, an E4 polypeptide or an E1B and E4 polypeptide prior to expressing a second polypeptide comprising an E1A polypeptide. However, it would have been obvious for the ordinary skilled artisan to make a choice of between a first polypeptide comprising an E1B polypeptide, an E4 polypeptide or an E1B and E4 because expression of the E1B and E4 sequence is essential for operation of the adenoviral replication system recited in the '210 claims. The claims are therefore obvious one over the other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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/Anne-Marie Falk/
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